Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project:** 20. Identification and Characterization of Regulatory Factors of the Human Telomerase Gene

7. **Start and End Date of Research Project:** 4/21/2010 - 9/30/2011

8. **Name of Principal Investigator for the Research Project:** Jiyue Zhu, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 124,080

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost

ZHAO, Yuanjun	Postdoctoral Scholar	100	7,247 (sal + fr)
JIA, Wenwen	Postdoctoral Scholar	100	1,083 (sal+fr)
CHEN, Longgui	Research Technician	100	39,500 (sal+fr)

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Zhu, Jiyue	PI	< 2 %

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes___X_____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Mechanism of Metformin Action in Normal and PCOS Theca Cells	XNIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	2/2012	$324,592	$319,723
Repression of the hTERT Gene During Cell Differentiation	XNIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	7/2011 7/13/2013	$316,725 $313,558	$313,558 $313,558

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X_____ No_____

If yes, please describe your plans:

We have and will continue to apply for the continuation of the NIH grant and other sources that arise.

12. Future of Research Project. What are the future plans for this research project?

The continuation of the NIH grant which these funds have made possible has enabled us to continue and expand our research.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male			1	1
Female				
Unknown				
Total			**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic			1	1
Unknown				
Total			**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian			1	1
Other				
Unknown				
Total			**1**	**1**

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes___X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This project enabled us to receive the grants listed above which allowed us to continue and expand our research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No_____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No_____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance

Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Our long-term objective is to determine the mechanisms of *hTERT* gene silencing during development and differentiation and its activation in cancer cells. The *hTERT* gene, encoding the limiting subunit of human telomerase, is developmentally regulated. It is highly expressed in pluripotent stem cells and most cancers but stringently repressed in most somatic cells. Despite intensive investigation of the *hTERT* gene regulation, *cis*-regulatory elements and *trans*-acting factors involved in its repression and activation remain to be elucidated.

Regulation of the *hTERT* gene expression is a complex process involving distal regulatory elements and chromatin reorganization. Our data demonstrated that the endogenous *hTERT* locus was embedded in a condensed chromatin domain in many somatic cells, including both telomerase-positive (Tel^+) and -negative (Tel^-) cells. In addition, we found that the *hTERT* locus in episomal states was not subjected to repression, whereas a chromosomally integrated version recapitulated its native promoter regulation, suggesting a vital role of chromatin environment in its tight regulation. Based on these findings, we *hypothesize* that (1) the establishment of a functional chromatin environment and local nucleosomal architecture is essential for hTERT repression; and (2) partial loss of repression leads to hTERT transcription during cellular immortalization.

In the first project, to study the mechanisms of hTERT repression, we have designed a genetic screening approach searching for novel factors involved in this repression in somatic cells using RNA interference. Our *specific aim* is,

Aim 1. Validation and characterization of novel repressors of the hTERT gene. In a recent screen for regulatory factors of the *hTERT* gene, we identified several candidates that are likely involved in the repression of the hTERT promoter. We plan to validate their regulation of the endogenous *hTERT* gene and determine their roles in telomerase regulation during cell differentiation.

Note: the following aims were added with DOH approval in August 2010:

In the second part of the project, we propose to study the developmental regulation of the hTERT gene. Whereas epigenetic mechanisms have been linked to gene activation/silencing and chromosomal stability, relatively little is known about how epigenetic memories are directed to and established on target DNA sequences, or *cis* regulatory elements, during cellular developmental processes and in response to extracellular environment. In a few exceptional cases, such as the well-studied chicken β-globin loci, many of the mechanistic evidences came from mutations found in human genetic diseases. An impediment has been the lack of genetically

modifiable reporter systems that readily provide sensitive and accurate assessment for the developmental regulation of target genes in mammalian cells. Hence, we propose to identify the *cis* elements responsible for the epigenetic regulation of the *hTERT* gene using the recombinase-mediated BAC targeting (RMBT) method and *in vitro* osteogenic differentiation of mESCs. In this proposal, we plan to generate additional evidence supporting our notion that the BAC reporter contains *cis* elements sufficient for the epigenetic hTERT regulation during the development of hTERT BAC transgenic mice. In addition, we also plan to construct a lentiviral acceptor vector for RMBT in mESCs. Our specific aims are:

Aim 2. Characterization of the hTERT BAC reporter in transgenic mice. To demonstrate that the BAC clone contains sufficient regulatory elements, we will determine the expression profile of the transgenic hTERT promoter during embryonic development.

Aim 3. Construction of a lentiviral acceptor vector. Because lentiviral viruses are not silenced in pluripotent stem cells, a lentiviral vector will be generated and used to establish mESC acceptor lines for RMBT.

Aim 1.
Determine the roles of a novel pathway in the repression of hTERT gene.

Our data in the application to NIH (2R01GM071725-06A1) demonstrated that knockdown of GeneA in the epigenetic gene repression pathway by siRNAs significantly induced hTERT transcription from both chromatinized BAC reporter and endogenous *hTERT* locus, suggesting this pathway play a critical role in hTERT repression. Thus, we have examined GeneB, GeneC, and GeneD, all known to function in this pathway, for their roles in the regulation of hTERT gene expression. A mixture of three siRNA duplexes against each of the four genes was transfected into a 3C167b (Tel^+) line containing an integrated H(wt) reporter. As demonstrated in the parent application, GeneA siRNAs induced hTERT transcription from the H(wt) reporter. Similarly, the siRNA duplexes against GeneB also significantly activated hTERT promoter in the H(wt) reporter (Figure 1), suggesting that GeneB was likely involved in hTERT repression. Although the initial experiment showed that siRNAs against neither GeneC nor GeneD affected hTERT transcription, additional experiments are being performed to determine whether their mRNAs or proteins are knocked down by these siRNA duplexes. In addition, it is also possible that both GeneC and GeneD need to be knocked down simultaneously in order to de-repress the hTERT promoter due to their functional redundancy.

In short, our data has provided additional evidence that the epigenetic gene repression pathway plays an important role in the repression of *hTERT* gene in somatic cells. The discovery of the involvement of this pathway will represent a significant advance in our understanding of hTERT silencing in somatic cells and will also help to elucidate the differential regulation of *TERT* genes in human and mouse cells.

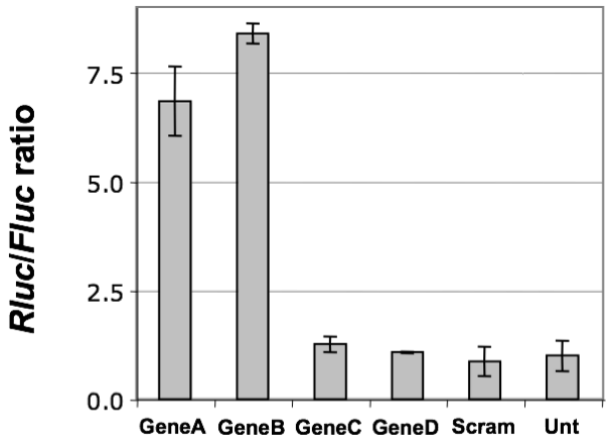


Figure 1. Effects on transgenic hTERT promoter activity by siRNAs against novel regulators. Mixtures of three siRNA duplexes against each gene were transfected into Tel^{+}/H(wt) cells using Lipofectamine RNAiMax reagent (Invitrogen) and luciferase activities were determined three days post-transfection. Data shown are averages of triplicate transfections in a 96-well plate and the experiment has been repeated multiple times.

Aim 2. Characterization of the hTERT BAC reporter in transgenic mice to demonstrate that the BAC clone contains sufficient regulatory elements.

Telomerase is tightly regulated in humans relative to mice, owing to the differential regulation of *TERT* genes. To explore hTERT regulation *in vivo*, we engineered mice with a 160-kb transgenic BAC spanning the *hTERT* locus with a *Renilla* luciferase (*Rluc*) cassette downstream of its promoter. Analysis of multiple founder lines revealed that the *Rluc* expression profile from the transgenic hTERT reporter locus reproduced that of the native *hTERT* gene in all tissues and organs examined, demonstrating that genetic sequence determined the species-specific developmental regulation of the *hTERT* gene and that mouse epigenetic and transcription machineries faithfully regulated hTERT transcription. Thus, these mice allowed detailed analyses of developmental hTERT regulation. Both the transgenic hTERT reporter and the endogenous *mTERT* locus were expressed in early embryonic stages and their mRNA levels progressively decreased throughout embryonic and postnatal development. Whereas hTERT transcription was much lower than mTERT expression in most organs, it increased significantly during postnatal development of thymus, testis, and ovary. In testis, the *Rluc* mRNA was enriched in elongating spermatids of seminiferous tubules. Additionally, the transcription of transgenic hTERT reporter, but surprisingly not the endogenous *mTERT* gene, was activated during Wnt1-induced mammary tumorigenesis, allowing the monitoring of tumor development via non-invasive bioluminescent imaging. Collectively, our results demonstrate that the hTERT transgenic reporter system recapitulates the developmental regulation of the *hTERT* gene in a

chromosomal position-independent manner and serves as legitimate model to explore telomerase regulation in the development of normal and neoplastic tissues *in vivo*. This work has been published in

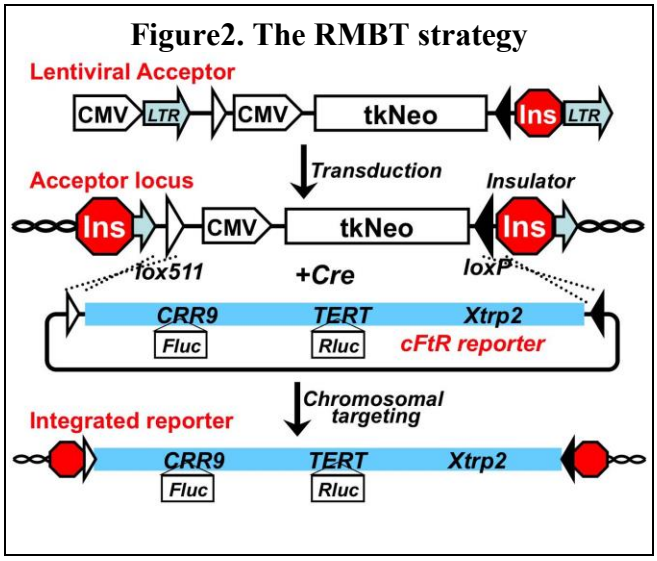
Jia, W., et al. A BAC transgenic reporter recapitulates *in vivo* regulation of human telomerase reverse transcriptase in development and tumorigenesis (2011) *FASEB Journal* 25(3):979-89.

Aim 3. Development of a genetically amendable system for studying the epigenetic regulation of the hTERT gene in mouse embryonic stem cells.

*Acceptor vector***.** Our published RMBT technique was a two-step procedure: generation of acceptor loci by retroviral transduction and Cre-mediated BAC integration (Figure 2) (Wang et al. Nucleic Acids Res 37(17):e111). Though successful in fibroblasts, the strategy was inefficient in ESCs due to retroviral silencing. Thus, we constructed a lentiviral acceptor vector, as lentiviruses are not silenced in ESCs. Briefly, a floxed CMV promoter/tkNeo cassette was used to replace eGFP in the lentiviral vector pLL3.7 and a 1.2-kb chicken β-globin insulator cHS4 inserted into the enhancerless 3' LTR. The resulting lentiviral vector is similar to the original retroviral vector pML-2 except for the lack of CreER. Upon transduction, the 3' LTR is copied to the 5' end, surrounding the acceptor locus with insulators and thus shielding it from potential chromosomal position effects (CPE).

Acceptor lines. One strain of HM1 mESCs, adapted to grow on gelatin-coated plates under feeder-free conditions for easier selection and clonal expansion, was transduced with the acceptor lentivirus at a low MOI (multiplicity of infection) to minimize multiple infections in a single cell. Neomycin-resistant colonies were isolated and genomic DNAs subjected to Southern analysis (Figure 3 A&B). Clones with single-copy proviral insertions (labeled by stars in Figure 3B) and normal karyotypes were chosen as acceptor lines.

BAC integration. Reporters 117B23-cFtR and 183M22-cFtR will be transfected into HM1 ESC acceptor lines, with a Cre-expressing plasmid pCAGGS (Figures 2), followed by a 3-day selection by puromycin (Puro) and a 2-day selection by ganciclovir (GCV). Drug-resistant colonies with both *Fluc* and *Rluc* activities will be expanded and their genomic DNAs examined by Southern analysis to identify correctly targeted clones. In the past six months, we have worked out the RMBT conditions in mESCs using a 14-kb BAC backbone vector (pBACpuroF). PCR analysis of junction sequences in Puro/GCV-resistant clones showed that at least two acceptor loci (HM1A1&A2) recombined with the vector readily (Figure 3 C&D).



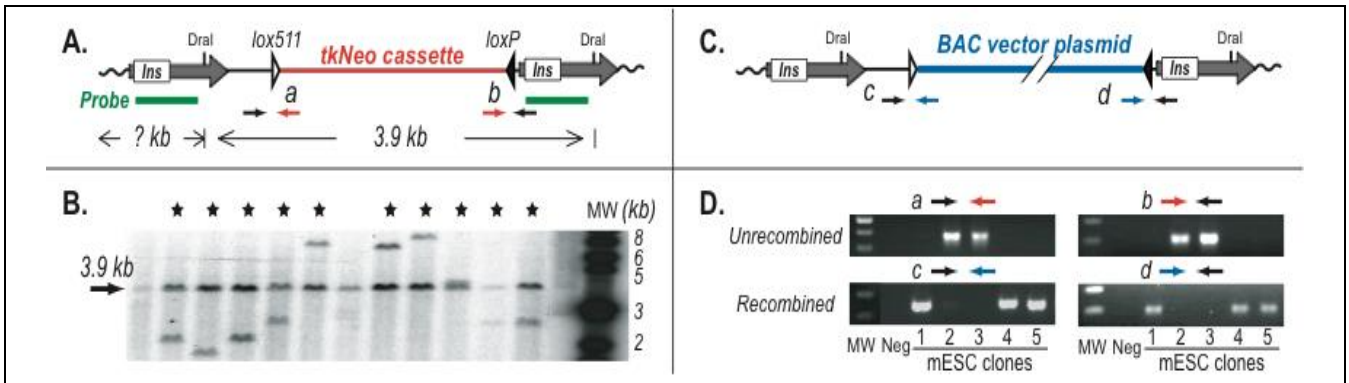


Figure 3. **BAC vector integration into an acceptor locus in mESCs (HM1A1) by RMBT**. (**A** & **C**) Diagrams of the acceptor locus before and after recombination. (**B**) Southern analysis of DraI-digested genomic DNAs to identity acceptor lines with single-copy lentiviral insertion, using LTR as probe (green). Multiple acceptor lines are obtained, as indicated by a variable sized band and a 3.9-kb fragment (labeled by stars). (**D**) Characterization of targeted mESC clones following RMBT with vector pBACpuroF, by PCR analysis of genomic DNAs. Small arrows (a, b, c, & d) denote primer pairs for junctions before (a & b) and after (c & d) targeting. Clones 1, 4, & 5 contained targeted locus.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04),

the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No_____

If yes, please describe your plans:

PI is no longer at Penn State.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable."

Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

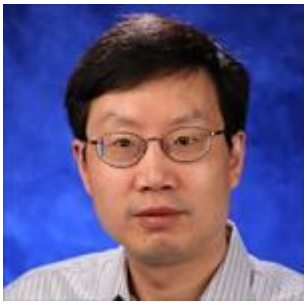
23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

Jiyue Zhu



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Phone	7175313597
Email	joz1@psu.edu

PREFERRED TITLE/ROLE: Associate Professor of Cellular and Molecular Physiology

SECONDARY APPOINTMENT(S)/ INSTITUTE(S)/ CENTER(S):
Penn State Cancer Institute

GRADUATE PROGRAM AFFILIATIONS:
Cell and Molecular Biology, Physiology, Genetics, Integrative Biosciences, MD/PhD degree program, Molecular Toxicology

EDUCATION:
Ph.D., Dartmouth Medical School, 1991
Postdoctoral Fellow, Harvard Medical School, 1991; Research Associate, 1992
Postdoctoral Fellow, University of California, 1993-1999

NARRATIVE:
Our laboratory studies the epigenetic and chromatin regulation of the human telomerase reverse transcriptase (hTERT) gene, which plays critical roles in stem cell self-renewal, aging, and cancer. Whereas telomerase mutations causes premature aging, its activation leads to limitless cell proliferation, a hallmark of all cancers. The ongoing projects focus on the identification of epigenetic elements and regulatory proteins involved in telomerase regulation during stem cell differentiation, nuclear reprogramming, and tumorigenesis, using models of normal and cancer

cells, adult stem cells, embryonic stem cells, induced pluripotent stem cells (iPSCs), and transgenic mice.

Publications listed below are automatically derived from MEDLINE/PubMed and other sources, which might result in incorrect or missing publications.

1. Jia W, Wang S, Horner JW, Wang N, Wang H, Gunther EJ, DePinho RA, Zhu J. A BAC transgenic reporter recapitulates in vivo regulation of human telomerase reverse transcriptase in development and tumorigenesis. FASEB J. 2011 Mar; 25(3):979-89. View in: PubMed
2. Zhao Y, Wang S, Zhu J. A multi-step strategy for BAC recombineering of large DNA fragments. Int J Biochem Mol Biol. 2011; 2(3):199-206. View in: PubMed
3. Mathew R, Jia W, Sharma A, Zhao Y, Clarke LE, Cheng X, Wang H, Salli U, Vrana KE, Robertson GP, Zhu J, Wang S. Robust activation of the human but not mouse telomerase gene during the induction of pluripotency. FASEB J. 2010 Aug; 24(8):2702-15. View in: PubMed
4. Zhu J, Zhao Y, Wang S. Chromatin and epigenetic regulation of the telomerase reverse transcriptase gene. Protein Cell. 2010 Jan; 1(1):22-32. View in: PubMed
5. Wang S, Hu C, Zhu J. Distinct and temporal roles of nucleosomal remodeling and histone deacetylation in the repression of the hTERT gene. Mol Biol Cell. 2010 Mar 1; 21(5):821-32. View in: PubMed
6. Zhao Y, Wang S, Popova EY, Grigoryev SA, Zhu J. Rearrangement of upstream sequences of the hTERT gene during cellular immortalization. Genes Chromosomes Cancer. 2009 Nov; 48(11):963-74. View in: PubMed
7. Wang S, Zhao Y, Leiby MA, Zhu J. Studying human telomerase gene transcription by a chromatinized reporter generated by recombinase-mediated targeting of a bacterial artificial chromosome. Nucleic Acids Res. 2009 Sep; 37(17):e111. View in: PubMed
8. Wang S, Zhao Y, Hu C, Zhu J. Differential repression of human and mouse TERT genes during cell differentiation. Nucleic Acids Res. 2009 May; 37(8):2618-29. View in: PubMed
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